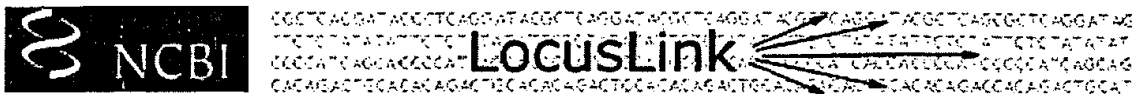

Homo sapiens Official Gene Symbol and Name (HGNC)

CMM: cutaneous malignant melanoma/dysplastic nevus

Locus Information — Submit GeneRIF for CMM ?

LocusID: 1243
Type: gene with protein product, function known or inferred
Alternate Symbols: DNS, MLM, CMM1
Alias: dysplastic nevus syndrome
OMIM: 155600
Phenotype: Malignant melanoma, cutaneous

Map Information ?

Chromosome: 1 **mv**
Cytogenetic: 1p36 HUGO

Additional Web Resources ?

GeneCard for CMM
GeneCard for DNS
Genes and Disease

To Top

Questions or Comments?
Write to the NCBI Service Desk
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*155600 Related Entries, PubMed, LinkOut

MELANOMA, CUTANEOUS MALIGNANT; CMM

Alternative titles; symbols

CMM1
MELANOMA, MALIGNANT
FAMILIAL ATYPICAL MOLE-MALIGNANT MELANOMA SYNDROME; FAMMM
MELANOMA, FAMILIAL; MLM
DYSPLASTIC NEVUS SYNDROME, HEREDITARY; DNS
B-K MOLE SYNDROME, INCLUDED

Gene map locus 1p36

TEXT

DESCRIPTION

Malignant melanoma is a malignant neoplasm of melanocytes, arising de novo or from a pre-existing benign nevus, which occurs most often in the skin but also may involve other sites.

CLINICAL FEATURES

Several writers (e.g., Moschella, 1961; Schoch, 1963; Salamon et al., 1963) commented on the usual fair complexion, blue eyes, and multiple ephelides in patients with familial melanoma.

In a questionnaire study, Kopf et al. (1986) found that a positive family history for melanoma was correlated with a younger age at first diagnosis in the proband, a smaller diameter of the lesion, lower Clark level, decreased frequency of nonmelanoma skin cancer, and reduced prevalence of noncutaneous cancer. (The Clark index refers to the level of invasion.) A comparison of monozygotic and dizygotic twins for melanoma might be important because of cases of melanoma in non-blood-related members of the same household (Robinson and Manheimer, 1972).

Lynch et al. (1978) suggested that a cutaneous marker indicative of susceptibility to malignant melanoma is characterized by large moles, variable in number, reddish brown to pink in color, and with an irregular border. Histologically, they show a bizarre intraepidermal pattern. The authors also described a melanoma family with distinctive freckling and dryness of the skin, suggesting xeroderma pigmentosum (278700) but with normal unscheduled DNA repair and a dominant pedigree pattern. Other malignancies such as colon cancer had an increased frequency in these families.

Clark et al. (1978), Greene et al. (1978), and Reimer et al. (1978) pointed out distinctive clinical and histologic features of the moles that are precursors of familial malignant melanomas. They termed these features the 'B-K mole syndrome' after the family names of 2 patients; later, Greene et al. (1980) and Elder et al. (1980) expressed a preference for the designation 'hereditary dysplastic nevus syndrome.' The same lesion underlies some cases of nonfamilial malignant melanoma. Greene et al. (1980) referred to this as 'dysplastic nevus syndrome, sporadic type.' The clinical features include between 10 and 100 moles on the upper trunk and limbs, and variability of mole size (from 5 to 15 mm), outline, and color. Histologically, B-K moles show atypical melanocytic hyperplasia, lymphocytic infiltration, delicate fibroplasia, and new blood vessel formation. Lynch et al. (1980) referred to this as FAMMM (familial atypical mole--malignant melanoma syndrome). Arndt (1984) and Greene et al. (1985) provided photographic illustration of the familial dysplastic nevus syndrome.

Lynch et al. (1980) studied 3 kindreds of the FAMMM syndrome. Father-to-son transmission was observed. One patient had 9 separate primary melanomas in 18 years. Expressivity was highly variable. Management is difficult because one cannot be certain which moles require biopsy and then, following histologic study, which require wide excision. The possibility of increased risk of cancer at other sites was raised. Hartley et al. (1987) described several cases of malignant melanoma in close relatives of children with osteosarcoma (259500) and chondrosarcoma (215300). They proposed that in certain families malignant melanoma may be a manifestation of the same gene defect that results in susceptibility to tumors characteristic of the SBLA syndrome (151623).

OTHER FEATURES

Tumor-specific antigens have been found in malignant melanoma (Hawkins et al., 1981; Pellegris et al., 1982).

INHERITANCE

Multiple authors have documented familial inheritance in malignant melanoma: see Cawley (1952); Smith et al. (1966); Andrews (1968). Katzenellenbogen and Sandbank (1967) described dizygotic twins with malignant melanoma.

Anderson et al. (1967) described malignant melanoma in at least 15 members of 3 generations of 1 kindred. Early age of onset and a tendency for multiple primary lesions were features. Lynch and Krush (1968) described 2 families with malignant melanoma in 2 generations in 1 family and 3 generations in the other. Anderson (1971) reported 36 pedigrees in which a total of 106 members had cutaneous melanoma. He noted that in addition to earlier age at onset and increased frequency of multiple primary lesions, familial cases have a higher survival rate than nonfamilial cases.

Rhodes et al. (1985) found that the prevalence rate of congenital nevomelanocytic nevi was 11 times greater in sibs of probands than in the general population. They had some families with 2 generations affected.

In the families with CMM studied by Greene et al. (1983), further studies (8,7:Bale et al., 1985, 1986) showed that dysplastic nevus (DN), a lesion known to be a precursor of melanoma, also segregates in an autosomal dominant manner. Pascoe (1987) challenged the concept of a single dominant gene as proposed by Bale et al. (1986). Bale and Chakravarti (1987) defended their conclusion.

Traupe et al. (1989) also challenged the autosomal dominant hypothesis for dysplastic nevus syndrome on the basis of the lack of a genetic equilibrium between eliminated and newly arising mutations. Happle et al.

(1982) had advanced arguments in favor of polygenic inheritance of dysplastic nevi: 1) lack of a consistent family pattern; 2) frequent sporadic occurrence of the trait; 3) continuous transition between ordinary and dysplastic nevi; and 4) analogy with an animal model.

Kraemer et al. (1983) found 4 persons affected with the dysplastic nevus phenotype. The risk of developing melanoma is not constant but increases with the number of melanoma patients in the family. This is a feature typical of polygenic inheritance.

Bergman et al. (1986) studied extensively affected kindreds in 'an ancient fishing village in the neighborhood of Leiden,' The Netherlands. Autosomal dominant inheritance of DNS was confirmed. In 6 pedigrees, 33 patients with melanoma occurred. Fifteen unaffected persons were identified as gene carriers by their position in the pedigrees.

PATHOGENESIS

Gilchrest et al. (1999) reviewed the role of ultraviolet radiation in the induction of melanoma. They pointed out that even among kindreds predisposed to multiple atypical melanocytic nevi and melanomas because of germline mutations in the CDKN2A gene (600160), retrospective analyses suggest that the incidence of melanoma has increased in recent generations, a phenomenon ascribed to the independent risk factor of increased sun exposure. Not only melanoma but also the more common skin cancers, basal cell and squamous cell carcinomas, are related to ultraviolet exposure. However, unlike the more common skin cancers, which are associated with total cumulative exposure to UV radiation, melanomas are associated with intense intermittent exposure. Thus, basal cell and squamous cell carcinomas occur most commonly in maximally sun-exposed areas of the body, such as the face and the backs of the hands and forearms, and in persons with almost daily and substantial lifetime exposure to UV radiation, such as farmers and sailors. In contrast, melanoma occurs most commonly in areas of the body exposed to the sun intermittently, such as the back in men and the lower legs in women, with relative sparing of more frequently exposed sites such as the face, hands, and forearms; it is most common in persons with predominantly indoor occupations whose exposure to the sun is limited to weekends and vacations. Indeed, the large increase in the incidence of melanoma in recent decades may be attributable to the ability of large numbers of people to travel long distances to obtain intense exposure to the sun in winter. The risk of melanoma is associated specifically with exposures that induce sunburn, and a history of 5 or more severe sunburns during adolescence more than doubles the risk. Gilchrest et al. (1999) suggested a biologic basis of these phenomena. The hypothesis was based on differences in response of keratinocytic stem cells and melanocytes to UV exposure. In melanocytes, a first high dose of ultraviolet radiation will cause substantial damage but not apoptosis; therefore, the melanocytes will survive to mutate and divide. Indeed, the appearance of freckles in children, often abruptly after high-dose sun exposure, is consistent with the thought that freckles represent clones of mutated melanocytes. In contrast, intermittent high-dose exposures to UV radiation result in loss of these cells, whereas repeated low-dose exposure would be expected ultimately to cause multiple mutations in the cells retained in the basal compartment and hence give rise to keratinocytic cancers.

CYTOGENETICS

In 4 of 5 cases of malignant melanoma, Trent et al. (1983) found chromosome alterations, including deletion and translocation in the long arm of chromosome 6, specifically in the 6q15-q23 region. They pointed out that the MYB oncogene maps to this region. Becher et al. (1983), reviewing cytologic findings in malignant melanoma in their own and reported cases, likewise pointed to a high incidence of structural aberration of 6q (segment q11-q31), whereas the short arm remains structurally unchanged, though its genetic material is often duplicated, as in the case of isochromosome-6p in one of their cases. These findings accentuate the interest, they pointed out, in the relationships found between specific HLA

haplotypes and familial malignant melanoma (Hawkins et al., 1981; Pellegris et al., 1982).

Pathak et al. (1983), Balaban et al. (1984), and Rey et al. (1985) also reported preferential abnormalities of chromosome 6. Hecht et al. (1989) found a marked increase in chromosomal rearrangements in dysplastic nevi from patients with CMM and in their normal-looking skin but not in their lymphocytes.

MAPPING

Linkage studies of DN and CMM showed lod = 3.857 at theta = 0.08. All families giving evidence on linkage were in coupling and the maximum likelihood estimate of recombination was not significantly different from 0 (8,7:Bale et al., 1985, 1986) Bale et al. (1985) excluded linkage of CMM to HLA.

In the Dutch family described by Bergman et al. (1986), Frants et al. (1989) and van Haeringen et al. (1989) excluded linkage with Rh; indeed, data from additional markers excluded the DNS gene from the entirety of 1p. Bergman et al. (1994) found in this family that a melanoma-associated gene was linked to several markers on 9p21. In a linkage analysis in which only melanoma patients were considered as affected, marker D9S171 showed a maximum lod score of 3.11 at theta = 0.0. After introducing family members with 10 or more, or 5 or more, atypical nevi as affected in addition to the melanoma patients, the maximum lod score rose to 4.88 at theta = 0.05 and 3.79 at theta = 0.07, respectively. Interestingly, the sharing of a unique 9p21 haplotype among most melanoma patients in the families from 2 different villages suggested that an old common mutation is present in the Leiden region.

Multipoint linkage analysis appeared to support the assignment of CMM to 1p (Bale et al., 1987). In 3 Utah kindreds ascertained through multiple cases of melanoma, Cannon-Albright et al. (1990) could find no evidence of linkage with the 2 markers most closely linked in the Bale study. Both melanoma alone and a combined melanoma/dysplastic nevus syndrome phenotype were analyzed. Furthermore, multipoint linkage analysis excluded the CM/DNS locus from an area of 55 cM. Bale et al. (1989) presented further evidence supporting assignment of the CMM locus to chromosome 1p36, 7.6 cM distal to PND and flanked by D1S47.

Dracopoli et al. (1989) found loss of heterozygosity at loci on 1p in 43% of melanomas and 52% of melanoma cell lines. Analysis of multiple metastases derived from the same patient and of melanoma and lymphoblastoid samples from a family with hereditary melanoma showed that loss of heterozygosity at loci on distal 1p is a late event in tumor progression rather than the second mutation that would occur if melanoma were due to a cellular recessive mechanism. In neuroblastoma and in type II endocrine neoplasia also, 1p loss of heterozygosity is frequent, suggesting that this loss is a common late event of neuroectodermal tumor progression. By multipoint linkage analysis of 6 families, Dracopoli et al. (1989) found evidence that the familial melanoma gene maps to 1p36 about 8 cm distal to PND (108780). The lod score was 5.42. Goldstein et al. (1993) extended the linkage studies to updated versions of these 6 families plus 7 new families. They concluded that there was 'significant evidence of heterogeneity,' and considered that this was responsible for the failure of some previous studies to confirm linkage to 1p in some families.

Millikin et al. (1991) used RFLPs to look for loss of constitutional heterozygosity (LOH) for markers on 6q. LOH on chromosome 6q was identified in 21 of 53 informative loci (40%). The chromosomal region bearing the highest frequency of 6q allelic loss was defined by the marker loci MYB (189990) and ESR (133430) located at 6q22-q23 and 6q24-q27, respectively. Possibly contradictory to chromosome 6 information is the report of Greene et al. (1983) of possible linkage to Rh (which is on 1p). A maximum lod score of 2.0 at theta 0.30 was observed.

Nancarrow et al. (1992) reviewed the contradictory findings of linkage in this disorder and presented studies of 7 Australian kindreds. Both Cannon-Albright et al. (1990) and Kefford et al. (1991) had questioned the validity of dysplastic nevi as a marker for familial melanoma and excluded linkage to markers on 1p when familial melanoma alone (symbolized MLM) was used as the phenotype. Several of the Australian families studied by Kefford et al. (1991) showed little or no history of dysplastic nevus syndrome or surgical removal of histologically characterized dysplastic nevi. Of the 7 other Australian kindreds studied by Nancarrow et al. (1992), 3 had the largest number of affected individuals reported worldwide. Because they also had families without dysplastic nevi and because the data used to calculate the parameters of the model used by Kefford et al. (1991) were estimated from a population-based survey, Nancarrow et al. (1992) used the latter model but also analyzed the data with the model of Bale et al. (1989). The Kefford model was applied to MLM alone and took into account variable penetrance with age and variable frequency of sporadic cases with age. With this approach, they excluded MLM from a 40-cM region that spanned the interval between D1S47 and PND and extended approximately 15 cM on either side of these markers to a total of 70 cM. In addition, they excluded a region of about 20 cM around the D1S57/MYCL1 (164850) loci at 1p32. Nancarrow et al. (1992) carried out linkage analysis in 3 large Australian melanoma pedigrees, using 172 microsatellite markers spread across all autosomes. Three additional smaller families were typed for 70 of the same markers. In 5 of the 6 families, they found lod scores between 1.0 and 2.3, which suggested localization of melanoma genes in proximity to some of the markers. This may indicate genetic heterogeneity since there was no marker for which all families gave significantly high lods. Their data provided the basis of an exclusion map; regions of chromosome 6, 9cen, and 10qter could not be excluded in these studies.

The cutaneous malignant melanoma locus on chromosome 1 has been designated CMM1. Several lines of evidence point to the existence of a second locus on chromosome 9 designated CMM2 (see 155601). There may be a third locus (CMM3) on chromosome 6 (Dracopoli, 1992).

Following up on previous linkage analyses of 19 cutaneous malignant melanoma/dysplastic nevi (CMM/DN) kindreds which showed significant evidence of linkage and heterogeneity to both chromosomes 1p and 9p, Goldstein et al. (1996) examined 2-locus hypotheses. The lod scores for CMM alone were highest using the single locus-heterogeneity model. They found much stronger evidence of linkage to 9p than to 1p for CMM alone; the lod scores were approximately 2 times greater on 9p than on 1p. A change in lod scores from an evaluation of CMM alone to CMM/DN suggested to the authors that a chromosome 1p locus contributed to both CMM and CMM/DN, whereas a 9p locus contributed more to CMM alone. For 2-locus models, the lod scores from 1p were greater for CMM/DN than for CMM alone. After conditioning on linkage to the other locus, only the 9p locus consistently showed significant evidence for linkage to CMM alone.

CLINICAL MANAGEMENT

The familial dysplastic nevus syndrome is a good example of a genetic disorder which lends itself to the practice of preventive genetics, i.e., preventive medicine, at the family level (Greene et al., 1985). Since 1960, mortality from cutaneous melanoma in the U.S. has risen more than mortality from any other cancer except carcinoma of the lung.

HISTORY

The earliest report may be that of Norris (1820). In describing a case of malignant melanoma, Norris wrote: 'It is remarkable that this gentleman's father, about thirty years ago, died of a similar disease. A surgeon of this town attended him, and he informed me that a number of small tumours appeared between the shoulders...This tumour, I have remarked, originated in a mole, and it is worth mentioning, that not only my patient and his children had many moles on various parts of their bodies, but also his own father and

brothers had many of them. The youngest son had one of these marks exactly in the same place where the disease in his father first manifested itself. These facts, together with a case that has come under my notice, rather similar, would incline me to believe that this disease is hereditary.' See commentary by Hecht (1989).

SEE ALSO

Bale et al. (1989); Bale et al. (1985); Bale et al. (1985); Becher et al. (1983); Dracopoli et al. (1987); Dracopoli et al. (1989); Elder et al. (1982); Fountain et al. (1992); Howell et al. (1984); Lynch et al. (1983); Ochi et al. (1984); Turkington (1965); Vasen et al. (1989); Wallace et al. (1973); Wallace et al. (1971)

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